Medical Staff Conference

Regulation of Hematopoiesis

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These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SANDE:* *Dr Desforges is one of those unusual leaders in hematology who is equally at home with erythrocytes, leukocytes and coagulation problems. She is Professor of Medicine at Tufts University School of Medicine, an associate editor of the* New England Journal of Medicine *and a productive scientist with about 100 publications in hematology. She has been voted outstanding teacher by medical students for eight years at Tufts and is the President of the American Society of Hematology. Dr Desforges showed her considerable clinical skills at our medical staff conference earlier and will now address us on the topic of "Regulation of Hematopoiesis."*

DR DESFORGES:† Hematologic disease is often expressed in a quantitative variation in elements of the circulating blood. The balance between production and destruction can be disturbed on either side. In the past, much attention has been given to physiologic and pathologic mechanisms controlling the rate of destruction of circulating elements in the blood. In cases of hemolytic anemia, for example, shortened erythrocyte survival may be due to an abnormal environment resulting in biochemical, oxidant or mechanical damage or to an abnormal immune response causing immunologic injury. Delineation of the mechanism in an individual case of hemolysis, therefore, has specific therapeutic implications. More recently, attention has been focused on mechanisms that may control the rate of production of cells by the marrow in normal and dyspoietic states. Abnormalities of production may involve one or more cell lines and may affect associated normal hematopoiesis. Impairment of hematopoiesis may occur on the one hand with aplasia induced by chemical or biologic mechanisms or, on the other, with suppression of normal growth due to infiltration by a malignant population. Such failure of normal hematopoiesis may result from impairment of the progenitor cell itself or from abnormalities of accessory cells that have a regulatory function. Again, defining a basis for impaired production in a given case has an important bearing on treatment.

Regulatory Network of Progenitor Cells

Studies during the past decade have provided some insights into the complex network controlling normal production and have also shown the pathologic effects of accessory cells in controlling stem cell growth in some disease states. Results of studies of in vitro hematopoiesis suggest that cell-cell interaction and feedback mechanisms normally play a role in controlling the production of leukocytes, erythrocytes and platelets to achieve a concentration within a narrow range. Effects of accessory cells and cell products in this hematopoietic process can be shown by in vitro culture of pluripotent stem cells or of the progenitor cells committed to a specific line. These systems provide a model for and allow study of cell proliferation and differentiation. In the semisolid cultures generally used, the number, size and cytologic characteristics of

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ABBREVIATIONS USED IN TEXT

B cells = lymphocytes that are programmed for immunoglobulin production
BFU-E = an early progenitor cell for the erythroid series, the burst-forming unit
CFU-E = a late progenitor cell for the erythroid series, the colony-forming unit
CFU-GM = a progenitor cell that is the colony-forming unit for granulocytes and monocytes
T cells = lymphocytes that are processed by the thymus. Subgroups are distinguished by specific surface antigens and functions

a generation of colonies can be evaluated. Using marrow or peripheral blood mononuclear cells as a source of progenitor cells, the environment provided in the culture determines which type of colony predominates.

Multipotent stems cells and committed stem cells, or progenitor cells, are found in the null fraction of circulating mononuclear cells. They lack recognizable characteristics of monocytes or B or T cells. Cohorts of other mononuclear cells—both monocytes and T cells—may, however, have a profound effect on the proliferation of these progenitor cells by either inhibiting or stimulating their growth.

CFU-GM Proliferation

Role of Monocytes and T Cells

The precursor that is the colony-forming unit for granulocytes and monocytes (CFU-GM) requires colony-stimulating activity to proliferate. Monocytes are a source of this, as are T lymphocytes.[1-5] The interaction between monocytes and T cells in providing this stimulus for progenitor cell growth may be complex.[3,6] Stimulation of T cells by a specific antigen and by a mitogen causes release of colony-stimulating activity from stimulated cells. The effect of mitogen is nonspecific. The effect of antigen in animal systems requires repeated exposure in the presence of interleukin 2, a cell product that stimulates T-cell proliferation to provide helper T cells. These antigen-specific T cells then provoke production of colony-stimulating activity from an Ia-restricted cohort of accessory cells. In this setting, then, the colony-stimulating activity is a side product of an immune response.[7]

The role of T cells in controlling release of the factor depends on the setting. Verma and co-workers have shown modulation of colony-stimulating activity production with varying treatment of the T cells.[6] Untreated T cells produce little colony-stimulating activity. Monocytes and T cells together produce greater amounts of the activity than monocytes alone. Incubating monocytes and T cells with a methanol extract of bacille Calmette Guérin increases colony-stimulating activity production whereas prior exposure of T cells to concanavalin A or thymosin decreases it. Other reports show inhibitory effects of T cells exposed to pokeweed mitogen and then assayed in culture. This effect has been attributed to activating T cells bearing IgG receptors and their possible interaction with other cohorts to suppress CFU-GM.[8,9] Mitogens such as phytohemagglutinin, however, stimulate production and release of colony-stimulating activity from T cells.[10-13] While such responses are in some ways analogous to the action of T-helper or T-suppressor cells in the immune response, there is no evidence that the effects on colony-stimulating activity production are mediated by the same cohorts that affect immune regulation.[14]

Feedback Regulation

A mature end product of the CFU-GM, the neutrophil, contains lactoferrin in its granules, the secretion of which appears to induce feedback inhibiting progenitor cell proliferation.[15] Broxmeyer has shown that this effect is the result of decreased production of colony-stimulating activity and Bagby and associates have suggested that lactoferrin-induced inhibition occurs via an effect on the T cell-monocyte interaction in the production of colony-stimulating activity.[3] Lactoferrin appears to prevent the stimulus provided by monocytes, probably a soluble factor, which provokes T cells to produce colony-stimulating activity. T cells sensitive to this stimulus express the Ia antigen, but do not appear to be confined to either of the T-cell cohorts designated by monoclonal antibodies OKT4 or OKT8 which, in general, define helper cells and suppressor cells, respectively. Ia antigen was first described in the murine transplantation antigen system, where it was found to be present on certain lymphocytes and monocytes. In humans, the DR antigen system is analogous and may be described as Ia-like. In this report, the term is used to describe the human antigen.

Ia antigen is found on T cells when they are activated or transformed and is not found when the cells are in a resting state. The presence of Ia here suggests that the cells have in some way become receptive and able to respond to the stimulus from monocytes. That this action of monocytes is not a unique effect on T cells is evident in recent work from this same group showing macrophages also inducing colony-stimulatory activity from neonatal skin fibroblasts. This colony-stimulating activity production is again sensitive to inhibition by lactoferrin.[16] Studies in our laboratory show eosinophils also inhibiting feedback of CFU-GM, but the mediator remains to be defined.[17]

The major role of monocytes in controlling myelopoiesis is further emphasized by the regulatory action of a prostaglandin of the E series, prostaglandin E_1, which is itself a product of monocytes. Prostaglandin E has been shown to be an inhibitor of CFU-GM,[18-21] but its effect is complex because it may also stimulate the production of colony-stimulating activity[22] and at the same time inhibit the response of the progenitor cells to its action. Progenitor cells may also express the Ia antigen, and only while expressing it do they appear to be susceptible to inhibiting regulation by prostaglandin E.[23] The presence of this antigen on their surface reflects that these progenitor cells are in S phase, and it may be the state of cell kinetics rather than the surface membrane antigen that dictates sensitivity to prostaglan-

din E. During in vitro incubation, the Ia antigen disappears. Prostaglandin E, in fact, stimulates its reexpression in this setting, making it susceptible to later inhibition by this same soluble factor.[24]

Monocytes also provide another monokine, acidic isoferritin, which regulates CFU-GM. Its activity was first described in specimens of leukemic marrow in which normal progenitor cell growth in vitro was suppressed. It appeared to be a product of leukemic cells[25] but has since been found in preparations of normal marrow and attributed to monocytes.[26] Acidic isoferritin acts directly on the progenitor cell, and does not appear to affect other accessory cells. The target, like that of prostaglandin E_1, appears to be those progenitor cells expressing Ia antigen.[27] Whether the Ia is simply a recognition site for isoferritin or whether it is a nonspecific reflector of susceptibility of the cells to inhibition is not clear. Recent studies in leukemic progenitor cells suggest that the antigen itself is necessary for the inhibitory effect both of prostaglandin E and of acidic isoferritin.[28]

In summary, proliferation of the monomyeloid progenitor cell, the CFU-GM, is regulated by several soluble factors released by monocytes and T cells and by their interaction (Figure 1). A series of feedback steps inhibits growth.

BFU-E Proliferation

Role of Monocytes and T Cells

A similar network surrounds proliferation of the primitive erythroid progenitor cell, the burst-forming unit, or BFU-E. The necessary conditions of culture include a source of burst-promoting activity—required for differentiating and proliferating the BFU-E—and the presence of erythropoietin, which allows maturation to recognizable erythroid cells. Both T cells and monocytes have been shown to produce burst-promoting activity.[29-34] Interaction of these cells, prostaglandin E and isoferritins may be involved in the proliferation of BFU-E. Monocytes and T cells have been shown to interact in producing burst-promoting activity[35,36]; some studies suggest that subsets of T cells have opposing regulatory effects on these progenitors.[37] The soluble mediator, prostaglandin E, differs in its effect on in vitro erythropoiesis vis-à-vis myelopoiesis. It stimulates rather than suppresses growth and differentiation of the BFU-E.[38-40] Although there is some controversy, it does not appear to affect accessory cells producing burst-promoting activity but acts only on the progenitor cells. The target of prostaglandin E seems again to be the Ia-receptive progenitor cell. This stimulatory effect differs from its inhibitory activity on CFU-GM and also contrasts with the parallel inhibition of BFU-E and CFU-GM induced by acidic isoferritin on the Ia-containing progenitor cells.[41]

Thus the erythroid progenitor cell is also regulated by monocytes and T cells interacting or independent in producing burst-promoting activity and in providing a modulating influence on growth or proliferation (Table 1).

Progenitor Cell Growth in Hematopoietic Disorders

Pure Red Cell Aplasia

The sensitivity of these progenitor cells to outside influence is evident in some hematopoietic diseases. In vitro study of progenitor cells from patients with disorders of production has shown an array of possible mechanisms that may affect hematopoiesis. A model for disease of a single progenitor cell is that of pure red cell aplasia in which there is a lack of production of only erythroid elements. In this syndrome the specific abnormality appears to vary with the associated clinical picture. In congenital pure red cell aplasia, most evidence supports a lack of the progenitor cell itself, though suppression by T cells has been suggested.[42,43] In contrast, when pure red cell aplasia is

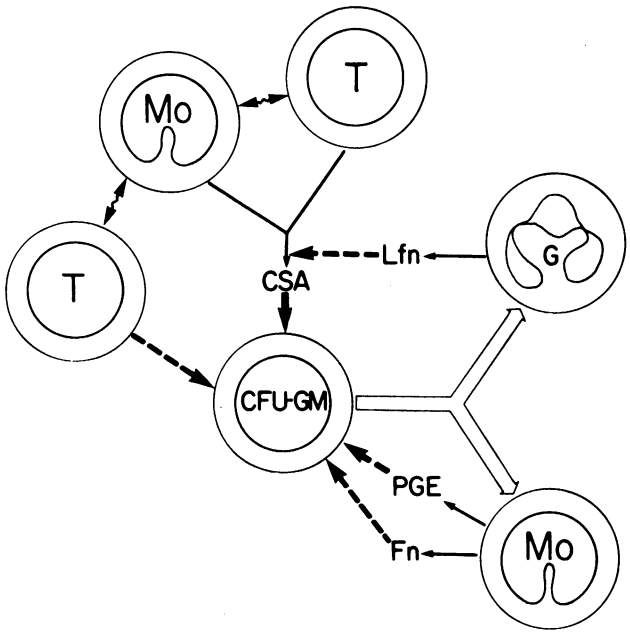

Figure 1.—Cellular control of progenitor cell growth (colony-forming unit for granulocytes and monocytes; CFU-GM). The wavy arrow (◄〰►) indicates interaction between monocytes (Mo) and T cells in producing an effect. The heavy arrow (⟵) indicates stimulation and the interrupted arrow (- - -►) inhibition. The thin arrow (⟶) indicates cell products that in turn inhibit or stimulate. Lactoferrin (Lfn) inhibits colony-stimulating activity (CSA) production; isoferritin (Fn) inhibits progenitor cells; colony-stimulating activity stimulates progenitor cells. PGE = prostaglandin E, G = granulocyte

TABLE 1.—*Effect of Cells and Cell Products on Progenitor Cells*

	CSA Production	*CFU-GM Proliferation*	*BPA Production*	*BFU-E Proliferation*
Monocyte	+	..	+	..
T cell	+	+ or −	+	+ or −
Prostaglandin E	+	−	..	+
Isoferritin	..	−	..	−
Lactoferrin	−	..	..	..

+ = increases, − = decreases, CSA = colony-stimulating activity, CFU-GM = colony-forming unit for granulocytes and monocytes, BPA = burst-promoting activity, BFU-E = burst-forming unit for erythroid series.

associated with the lymphoproliferative disorder, progenitor cells may be present, but accessory cells are at fault.[44] In the latter cases, production of burst-promoting activity by T cells is diminished. Following treatment of the lymphoproliferative disorder in these patients with associated remission of pure red cell aplasia, burst-promoting activity production in the presence of T cells is restored to normal. In some cases, a cellular inhibitor of the more mature erythroid progenitor, CFU-E, has also been described and appears to fall in the T-cell cohort.[45] Genetically restricted suppression of BFU-E by the leukemic cells has been found in a patient with pure red cell aplasia and a T-cell lymphoproliferative syndrome.[46] Whether such inhibitory cells are an expansion of a normal inhibitory cohort or an autoimmune response is not known, but the effect diminishes with chemotherapy for the lymphoproliferative disorder.

In cases of idiopathic acquired pure red cell aplasia, autoimmunity has been demonstrated.[44,47] A circulating immune globulin has been found to inhibit BFU-E growth in the presence of complement in such cases. The target cell for this immunoreaction has not been precisely identified and could be either a progenitor or an accessory cell. In these cases progenitor cells and accessory cells function normally when the patient's serum is removed from the system. Again, successful treatment of the syndrome is associated with normal results of in vitro culture in the presence of the patient's serum.

Infection

In patients with anemia associated with histoplasmosis, Zanjani and colleagues have described suppression of erythroid colony growth in the presence of marrow macrophages.[48] Moreover, they were able to attribute the effect to a soluble factor released upon incubation of monocytes. Following cure of the disease, the inhibitory activity could no longer be shown. One may postulate that this is a model for the anemia of chronic disease, in which there may be an abnormality in monokine production—that is, acidic isoferritin—or in monocyte-T cell interaction, resulting in suppression of progenitor cell growth.

Neutropenia

In vitro studies have also provided insight into the possible pathogenesis in cases of neutropenia. T lymphocytes have been identified as a source of inhibition in some cases,[49,50] but B cells may also play a role by producing antibody to CFU-GM.[51-52] In most reports, in vitro studies have been carried out using bone marrow or peripheral blood mononuclear cells, rather than isolated cohorts of cells. Evidence for inhibition is provided by observing the effect on progenitor cell proliferation of removing or adding T cells. One might postulate that the inhibitory action of these T cells is directed toward the progenitor cell itself, or, instead, toward another accessory cell in the regulatory network. Suppression of CFU-GM by T cells could be due to an imbalance of physiologic forces or to a pathologic autoimmune mechanism. In one case of neutropenia associated with tuberculosis described by Bagby and Gilbert, suppression of CFU-GM by T cells was no longer evident after cure of the disease.[49] Evidence for autoimmunity is more clear-cut in those cases in which a circulating immune globulin rather than a T-cell cohort has inhibited CFU-GM growth.

Aplastic Anemia

Aplastic anemia also shows varied in vitro culture characteristics, which suggest multiple causes. In many cases, a cell culture shows simply a lack of progenitor cells. In some, however, the proliferation of CFU-GM or BFU-E is improved when autologous T cells are removed, suggesting inhibition by these T cells.[53-55] In these cases, co-culture experiments in which a patient's T cells are added to normal progenitor cells and vice versa suggest that patients' T cells are inhibitory to normal progenitor cells as well. One must interpret such co-culture experiments with caution, however, because previous exposure to blood products in the patient may result in a cellular immune response that could include cytotoxic response to donor progenitor cells.[55] Few studies have been carried out to identify the subset of T cells involved in progenitor cell inhibition, but it appears not to be confined to the suppressor cell fraction as defined by an OKT8 antigen.

Leukemia

Regulators may also play a role in suppressing normal myelopoiesis and erythropoiesis in leukemia. The relative insensitivity of leukemia progenitor cells to inhibition by acidic isoferritins, the leukemic inhibitory activity of Broxmeyer,[25] may give the malignant cells a growth advantage over normal progenitor cells. Similarly, the myeloid progenitors in cases of chronic myelocytic leukemia are less sensitive than those in normal persons to the "physiologic" inhibitory effect of prostaglandin,[22] a fact that could account for replacement of normal marrow with leukemic clones in this disease.

In cases of acute leukemia, in vitro growth characteristics of progenitor cells are abnormal. In the few colonies present, blast cells predominate and most of the growth is confined to small clusters. Differentiation is lacking. In preleukemic states, alteration of growth characteristics may evolve during the period of observation.[56] These in vitro abnormalities appear to correlate with the aggressiveness of the underlying process and may be the harbinger of leukemic transformation.

Hypereosinophilic Syndrome

In cases of proliferative disease, one might postulate an atypical response to normal regulators or modulation of growth induced by a shift in regulatory activity. In some cases of hypereosinophilic syndrome, the mononuclear cells have stimulated the production of an increased proportion of eosinophils. In other cases, an increased proportion of progenitors committed to eosinophilic differentiation has been described.[57] While these findings may be epiphenomena of this complex

TABLE 2.—*Possible Mechanisms of Deficient Hematopoiesis*

Decreased number of progenitor cells
Inadequate network of accessory cells
Inappropriate suppression by regulatory cells
Autoimmune suppression via cytotoxicity or antibody
Impaired production of stimulatory factors
Selective advantage of abnormal cells not subject to feedback inhibition

syndrome, the results of in vitro studies in this syndrome suggest a role in vivo for the cellular regulatory network.

Thus, in vitro culture of progenitor cells from patients with disorders of the marrow may reveal disturbances in the regulation of their growth. These disturbances may reflect abnormalities in the interaction among accessory cells, both monocytes and T cells, or insensitivity of progenitors to the physiologic regulators involved. In some cases data suggest that an imbalance of normal regulator cells may induce suppression of progenitor cells; in others, the inhibitory effect is consistent with cellular autoimmunity (Table 2). Such studies may give insight into an underlying disease process and can provide a rationale for the treatment selected.

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